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November 22, 1996

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Office of Naval Research
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Arlington, VA 22217-5660

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RE: Grant Number: N00014-95-10071
Professor Robert Alfano

Dear Dr. Ackleson:

Enclosed please find a copy three (3) copies of the Annual Performance Report for the above referenced grant.

Sincerely,

Regina Masterson

Regina Masterson
Director

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1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	November 1996	Progress Report 12/1/95 - 12/1/96

4. TITLE AND SUBTITLE
Time-resolved Near Infrared Optical Tomography

5. FUNDING NUMBERS
ONR #R&T Project Code 3220P03---01
Grant #N00014-95-0071

6. AUTHOR(S)
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8. PERFORMING ORGANIZATION REPORT NUMBER
RF447349

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Office of Naval Research
800 N. Quincy Street
Arlington, VA 22217

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES
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12 b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

The report covers the results obtained in developing theoretical approach and experimental procedure based on detecting early arriving light to characterize inhomogeneities in turbid media with a spatial resolution of the order of mean transport free path or smaller.

14. SUBJECT TERMS
photon migration, multiple scattering, time-resolved optical tomography, non-Euclidean diffusion equation.

15. NUMBER IF PAGES 15

16. PRICE CODE

17. SECURITY CLASSIFICATION OR REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
UNCLASSIFIED	UNCLASSIFIED	UNCLASSIFIED	UL

PROGRESS REPORT
ONR - FY 1996
Dec. 1, 1995 - Dec. 1, 1996
Title: Time-resolved Near Infrared Optical Tomography

ONR # R & T Project code 3220P03.....01, Grant # N00014-95-0071
CUNY RF # 447349

PI: R.R. Alfano.
Researchers: A.Ya.Polishchuk(Theory), F. Liu(Expt.), B.B.Das(Expt.), J.Dolne (exp)
Grad. Students: M. Zevallos, Y.X. Shan.

Goals:

To develop theoretical models and experimental procedures based on the detection of early arriving light to characterize inhomogeneities in turbid media in multiple scattering regime with spatial resolutions on the order of transport mean free paths (1-2 mm for biological tissues and highly scattering media).

Objectives:

During the reported period the following objectives were pursued:

1. to investigate the limits of applicability of the diffusion approximation (DA) for source detector distances large compared with photon transport mean free paths (where the DA is commonly believed to hold), and show that for higher frequency modes of photon migration and/or when absorption is about ~10% of the extinction, the DA becomes a progressively approach as the source detector distance increases.

2. to develop a new approach free from this drawbacks of DA.

3. to clarify the use of non-Euclidean diffusion (NED) equation especially tailored to describe non-diffusive features of photon migration in highly forward scattering media and to show the relationship between NED and the more general theory of radiative transfer (Boltzman equation).

4. to develop a path integral solution of the NED equation in the case of macroscopically inhomogeneous turbid media.

5. to perform a series of time-resolved experiments to check on the predictions of the NED equation against the intensity temporal profiles of scattered light measured at various distances between the source and the detector.

6. to investigate the non-diffusive nature of photon paths in turbid media by analyzing the experimental results using the NED equation and find out the potential of this equation to improve the resolution in future optical tomographic reconstruction.

Approach:

A close interaction between theory and experiment underlies our efforts to understand fundamental features of photon migration in turbid media, in order to improve the resolution in optical tomography.

The experimental part of the program was based on the measurement of temporal intensity profiles of the scattered light in turbid media using 100 fs laser pulses and a streak camera with 10 ps resolution. The turbid media used were biological samples like chicken breast tissue as well as model random media with monitored scattering and absorption properties: aqueous intralipid solutions and polystyrene bead suspensions.

In the theoretical part of the program numerical solution of the radiative transfer equation was used to investigate various generalizations of the diffusion equation including a new scalar-wave diffusion equation(SWDE) introduced in the course of this study. This part of the program was aimed at achieving a better description of photon migration in isotropically scattering media at large distances for high frequency diffusive modes and/or with absorption exceeding ~10% of the total extinction.

The concept of *photon diffusion on the velocity sphere and non-Euclidean path integral technique* both introduced in the frame of this grant underlie our analysis of non-diffusive features of photon migration in multiple scattering regime in highly forward scattering media. This approach was used to interpret time resolved experimental data, which demonstrate the existence of 'preferred' photon paths on scales of the order l_t (or smaller) in highly forward scattering random media.

Tasks Completed:

The tasks completed during this period follow.

Scalar wave diffusion equation(SWDE), was derived to describe the non-diffusive effects taking place at large distances from a source. SWDE has been shown to be superior to other available modifications of the diffusion equation to describe non-diffusive effects in isotropically scattering media (publication [3]).

The new concept of photon paths in highly forward scattering media was investigated using time-resolved experiments and the theory derived from non-Euclidean diffusion equation (NED). NED-based concepts of average and most probable ("Fermat") photon paths were successfully used to interpret the experimental results which demonstrate in contrast to the predictions of the diffusion theory, that photons "prefer" certain paths on a scale on the order of transport mean free paths (publications [1], [4]).

Time-and-angle-resolved experiments have demonstrated that the non-diffusive effects in photon migration are appreciable even at distances as large as 10-15l_t (20-30 mm) from the source (publications [2], [5], [6]).

Comparison of the above time resolved data with the results based on NED has demonstrated the potential of NED to describe the nondiffusive multiple scattering effect on photon migration in turbid media (publications [2], [6], [7]).

Results:

The following highlights our results:

Photon density modes beyond the diffusion approximation in a turbid medium with isotropic scatterers.

Various modifications of the diffusion model, available to date, designed to describe photon migration in scattering and absorbing media are summarized in the following equation:

$$\alpha\frac{\partial^2 N}{\partial t^2}+(\nu+\beta\nu_a)\frac{\partial N}{\partial t}-\frac{c^3}{3}\Delta N+\nu_a(\nu+\gamma\nu_a)N=0 \qquad (1)$$

for the photon number density $N(\vec{r},t)$. Here ν and ν_a are the transport and absorption collision frequencies. Different sets of numerical parameters $\{\alpha,\beta,\gamma\}$ corresponding to different models can be found in the literature: {0,0,0} (Furutsu, 1994), {0,1,1} (Paterson, Chance, Wilson, 1989), {1,2,1} (Ishimaru, 1989, Kashke, 1993) and {1/3, 2/3,1/3} (Lax, 1993, Morse &Feshbach, 1963). Starting with the general radiative transfer equation we have shown than none of the above versions of Eq.(1) is actually valid when used in non-diffusive domain, and a better new equation, called *Scalar wave Diffusion Equation (SWDE)* was derived. SWDE coincides in form with Eq.(1), but the set of coefficients $\{\alpha,\beta,\gamma\}$ is totally different: $\{\alpha,\beta,\gamma\}$ = {1/5,2/5,1/5}. To check the available versions of Eq.(1) and SWDE, *analytical solutions* of these equations N were compared with a numerical solution N_E of the exact radiative transfer equation for the intensity modulated source η switched on at a time t=0 :

$$\eta=\frac{1}{4\pi}\theta(t)\delta(\vec{r})exp(i\omega t) \qquad (2)$$

Relative changes in amplitude $\Psi=(|N|-|N_E|)/|N_E|$ are plotted versus ω/ν for source detector distance r = 25 l_t (Fig 1a) and r = 50 l_t (Fig 1b). The parameter ψ shows how close an approximate solution is to the reference N_E. As it is clear from Fig 1, the SWDE solution is much closer to the exact numerical solution, N_E, than any other model.

Note that the absorption collision frequency ν_a is completely equivalent to the parameter p in the Laplace transform of the experimental temporal profiles: $I(p)=\int_0^\infty e^{-pt}I(t)dt$. When $p=i\omega$ is an imaginary number, this corresponds to an

intensity modulated probing photon beam. High values of $|p| \approx 0.1\nu$ select early arriving light and correspond to smaller blurring. Therefore SWDE may lead to an improved resolution when used in early-light-based tomography.

A generalization of SWDE to the case of anisotropic scattering modes is to be considered separately.

Theory and experiment on ultrashort pulse non-diffusive propagation in highly forward scattering media.

Time-and-angle resolved intensity measurements of scattered light were using femtosecond laser pulses at 625 nm in a highly forward scattering medium at various source-detector distances much larger than l_t. The detector was placed in the direction of initial laser beam propagation, and orientation of the fiber was altered (Fig 2a, inset). The medium was 0.16% (by weight) suspension of 1.01 μm polystyrene spheres in water with l_t =2mm , la = 300mm, g = 0.93.

Fig. 2 shows the experimental results for various source detector distances. Note the absence of ballistic component for highly forward scattering media. Early arriving light is represented by snake photons. One may note that even at distances as large as 10-15 l_t (20-30 mm) angular distribution of light is much too far from being isotropic. Highly isotropic light distribution is a condition required for the diffusion approximation to be valid. These results show that diffusion approximation (DA) is hardly a reliable tool for high resolution optical tomography. The above experimental data were used to check on predictions based on non-Euclidean diffusion equation (NED), a possible alternate to DA.

Approximate solution to the non-Euclidean diffusion equation

During the reported period we have found approximate analytic solution to the NED:

$$\frac{\partial n}{\partial t} + \vec{s}\vec{\nabla}_r n - D_s \Delta_s n + \nu_a n = \delta(t)\delta(\vec{r})\delta(\vec{s} - \vec{s}_0) \qquad (3)$$

for the specific photon number density $n(t, \vec{r}, \vec{s})$ as a function of time t, position r, and velocity of photons s. In NED, Eq (3) scattering is described in terms *of photon diffusion on the velocity sphere*, where $D_s = c^4/6D$ is the photon diffusion coefficient on the velocity sphere expressed in terms of the ordinary 3D-diffusion coefficient D. We have found exact path integral solution of Eq(3) and analytically calculated this path integral to obtain the photon number density $N(\vec{r}, t) = \int d\vec{s} n(t, \vec{r}, \vec{s})$ using cumulant expansion in random process theory:

$$N(\vec{r}, t) = \frac{1}{\sqrt{(4\pi)^3 \det \Delta_{\alpha\beta}}} * exp\left\{-\frac{1}{4}\Delta^{-1}_{\alpha\beta}(\vec{r} - \vec{r}_c)_\alpha (\vec{r} - \vec{r}_c)_\beta\right\} e^{-\nu_a t} \qquad (4)$$

In Eq.(4), $\vec{r}_c(t) = \vec{s}_0(l_t / c) f_{l_t}$

$$\Delta_{\alpha\beta}(s_0 t) = \frac{l_t^2}{2}\delta_{\alpha\beta}(\frac{2}{3}\tau - f_1 + \frac{1}{9}f_3) + \frac{l_t^2}{2c^2}(s_0)_\alpha (s_0)_\beta (f_1 - \frac{1}{3}f_3 - f_1^2),$$

$$\tau = \frac{ct}{l_t}, \quad f_n = 1 - exp(-n\tau).$$

Eq 4 describes ultrashort pulse propagation represented as translational motion and spread of an initially point-like photon cloud launched in $\vec{s}_0$ direction. In Fig.3 the solution $N(\vec{r}, t)$ to Eq (4) is compared with the experimental results of Fig.2. The corresponding angular-dependent experimental profiles were integrated over all detector orientations to result in experimentally estimated photon number density. The experimental results confirm superiority of NED to DA in describing the early arriving light intensity and the whole temporal profile. Note that the approximate solution takes causality principle into account qualitatively. Obtaining analytical results for NED-based specific number density $n(t, \vec{r}, \vec{s})$ and its direct comparison with experimental data are under way. We also plan to find exact analytic representation for early portion of scattered light intensity with the causality principle taken into account exactly. These results may be used as a basis for future early-arriving-light tomography.

NED and nondiffusive structure of photon path in random media.

To examine the photon path pattern, time resolved intensity measurements of scattered light for a fixed source(S)-detector(D) arrangement have been used to determine the position at which a small absorbing object equidistant from the source and detector produces maximum effect on the detectors readings. Launching and collecting fibers were parallel to each other and perpendicular to SD line. The experiment revealed in contrast to the predictions of the diffusion theory, that photons traverse certain *curvilinear* paths between the source and the detector. These results can be interpreted in terms of average photon trajectory $\vec{r}_a(t|T)$ between a source and a detector, corresponding to a certain total travel time T. Note that $\vec{r}_a(t|T)$ in diffusion approximation is an exactly straight line between a source and detector. The point on $\vec{r}_a(t|T)$ for t = T/2 is the equdistant from the source and the detector.

We have used the analytical solution for the NED, Eq(4), to estimate $\vec{r}_a(t|T)$:

$$(\vec{r}_a(t|T))_i = (\Delta(\vec{s}_0, t) + \Delta(\vec{s}_{f0}, T-t))^{-1}_{ij} * (\Delta_{jk}(\vec{s}_f, T-t)\theta(t)s_{ok} + \Delta_{jk}(\vec{s}_0, t)(R_{fk} - \theta(T-t)s_{fk})) \quad (5)$$

Here $\vec{R}_f$ is the position of the detector with respect to the source,. $\vec{s}_0, \vec{s}_f$ are the initial and final velocities of photons ($\vec{s}_f = -\vec{s}_0$), $\theta(t) = (l_t/c)f_1(t)$, and functions $f_i(t)$ and $\Delta_{ij}(\vec{s}_0, t)$ were determined in connection with Eq.(4).

Fig 4. shows calculated average photon paths corresponding to the source-detector distance R=22mm and travel time T=157ps for various values of l_t . The value l_t = 15mm corresponds to the condition of our experiment. The cross (x) shows the experimentally determined position of the object corresponding to the maximal decrement in the detector reading. Satisfactory agreement of the theory and the experiment can be noted. When the ratio l_t/L is not small $\vec{r}_a(t|T)$ coincide with the most probable (Fermat paths $\vec{r}_F$). As the ratio l_t/T decreases the population of path increases and $\vec{r}_a$ deviate from $\vec{r}_F$ toward SD line in accordance with experimental observation of smaller l_t.

ACCOMPLISHMENTS:

1. Introduced and tested was a new scalar-wave-diffusion equation(SWDE) aimed at describing nondiffusion effects in a turbid media with isotropic scatterers for frequency modulation and time resolved studies.

2. Time and angle resolved experiments demonstrated that non-diffusive effects in photon migration are appreciable at distances as large as 10-15 l_t (20-30 mm). These effects promise to be important for early light tomography applications.

3. Comparison of time-and-angle-resolved experiment with the non-Euclidean diffusion equation(NED) introduced earlier showed that NED can be regarded as a feasible approach to describe nondiffusive photon path patterns in highly forward scattering media.

Publications.

[1] **P** - Polishchuk A.Ya. and Alfano R.R, 1996: Photon diffusion on the velocity sphere, Optics letters, 21, 916-919.

[2] **P** - Polishchuk A. Ya.; Zevallos M., Liu F., and Alfano R. R., 1996: Generalization of Fermat Principle for photons in random media: The least mean square curvature of paths and photon diffusion on the velocity sphere, Physical Review E, 53, 5523 -5526

[3] **P** - Polishchuk A.Ya, Gutman S., Lax M., Alfano R.R., 1997: Photon density modes beyond the diffusion approximation: scalar wave-diffusion equation, J. Opt. Soc. Am. A., 14, No 1

[4] **PS** - Polishchuk A. Ya.; Dolne J., Liu F. and Alfano R.R., 1996: Average and most probable photon paths in random media., Optics Letters

[5] **IC** - Polishchuk A. Ya.; Dolne J, Zevallos M.; Liu F. and Alfano R. R., 1996: Fermat Photons: Path Propagation and Imaging in Turbid Media, Advances in Optical Imaging and Photon Migration, OSA, March 18-22, Orlando, FL

[6] **R** - Zevallos M., Liu F., Das B.B., Polishchuk A.Ya., and Alfano R. R., 1996: Angular Dependence of the Intensity Temporal Profiles of Scattered Pulses in Diffusive regime, OSA TOPS on Advances in Optical Imaging and Photon Migration, 2, 21-24.

[7] **R** - Polishchuk A. Ya.; Dolne J, Zevallos M.; Liu F. and Alfano R. R., 1996: Fermat Photons: Path Propagation and Imaging in Turbid Media, OSA TOPS on Advances in Optical Imaging and Photon Migration, 2, 14-17

Interaction with optical imaging community

Quotation of our papers published in the frame of this grant in 1996:

1. L.Yang, J.U.Beecham 1996: Time resolved Anisotrophy Spectroscopy and Imaging theory Scattering Media using Most Favorable Fermat Photon Paths,Biophysical Journal,338. *(the idea of most probable photon paths was used to interpret experimental results)*

2. S.B.Colak, H.Schomberg, G.W.'t Hooft, M.B.Van der Mark, 1996: Optical Back Projection Tomography is Heterogeneous Diffusive media, OSA TOPS on advances in optical Imaging and Photon Migration, V2, 282. *(the idea of most probable photon paths was discussed)*

The following groups requested information about our work done under this grant:

1. George Weiss (National Institute of Health)
2. Mark Brezinski (Massachusetts general Hospital)
3. Michael Feld (Massachusetts Institute of Technology)
4. Norman McMormick (University of Washington)
5. Arjun Yodh (University of Pennsylvania)
6. Steve Jacques (Oregon Medical Laser Center)

Figure Captions

Fig.1 Comparison of the numerical solution of the radiative transfer equation N_E with the solution N, corresponding to the scalar-wave-diffusion equation and the different modification of Eq(1). Relative change in amplitude $\Psi = (|N| - |N_E|) / |N_E|$ is plotted: 0 - exact numerical solution N_E, 1-SWDE, 2-Ishimaru, 1989, Kashke, 1993, 3-Paterson, Chance, Wilson, 1989, Fishkin, Gratton, 1993; 4-Furutsu, 1994; 5-Lax, 1993, Morse & Feshbach, 1963. 2' corresponds to the curve 2 scaled as 1:2500. (a) source detector distance r = 25lt, $\nu_a = 0$; (b) r =50lt, $\nu_a = 0.1\nu$.

Fig2. Intensity profiles measured at various source detector distances r and for various orientations of the detecting fiber: (a) r = 5lt, (b) r = 7lt, (c) r = 10 lt, and (d) r = 15lt, The inset shows the geometry of the experiment.

Fig.3 (a) Comparison of the measured and calculated NED-based and DA-based photon number density profiles N(t) at $r=5l_t$; (b) Full width half maximal of N(t) and various distances; (c) T_p position of the maximum of the N(t) curve; (d) $I_p(r)/I(r=15l_t)$ relative amplitude of the N(t) curve. The most probable (Fermat) path is indicated by symbol F.

Fig 4 Calculated average photon paths corresponding to the source-detector distance R=22 mm and travel time T=157ps (overall path length 35 mm) for various values of l_t : (1) 15 mm; (2) 9 mm; (3) 4.5 mm; (4) 0.5 mm. The cross corresponds to the experimental data taken at l_t= 15mm.

STATISTICS:

1) Number of papers published in refereed journals	3
2) Number of papers submitted or in press, refereed journals	1
3) Number of books or chapters published, refereed non-serial publications	0
4) Number of books or chapters submitted or in press, refereed non-serial	0
5) Number of invited presentations at scientific conferences	1
6) Number of contributed presentations at scientific conferences	3
7) Number of technical reports and papers in non-refereed journals	2
8) Number of undergraduate students supported (at least part time)*	0
9) Number of graduate students supported (at least part time)*	0
10) Number of post-docs supported (at least part time)*	2
11) Number of other professional personnel supported (at least part time)*	0
12) Number of female grad students	0
13) Number of minority grad students	2
14) Number of Asian grad students	1
15) Number of female post-docs	0
16) Number of minority post-docs	1
17) Number of Asian post-docs	1

* 'Part time' means that at least 25% support this year on this ONR grant. NOTE: Minorities include Blacks, Aleuts, American Indians and Hispanics only.

Figure 1a

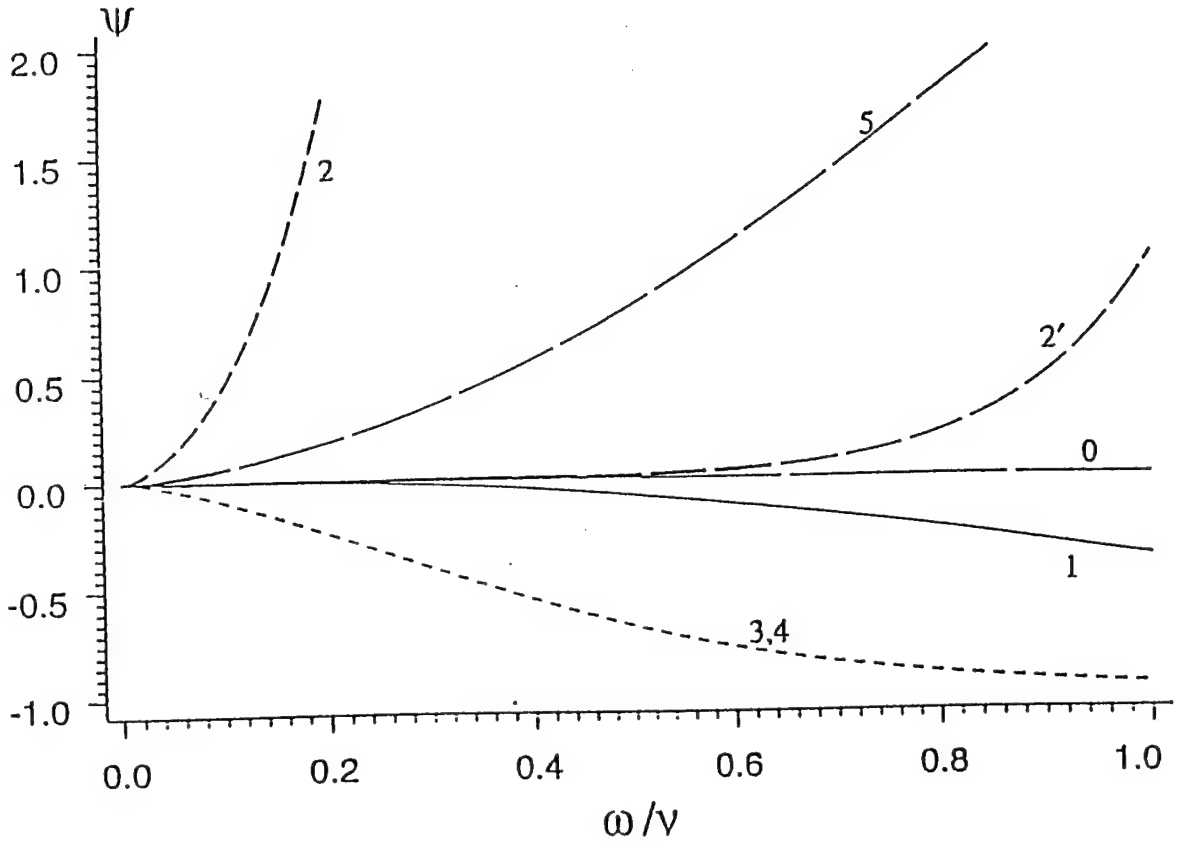


Figure 1b

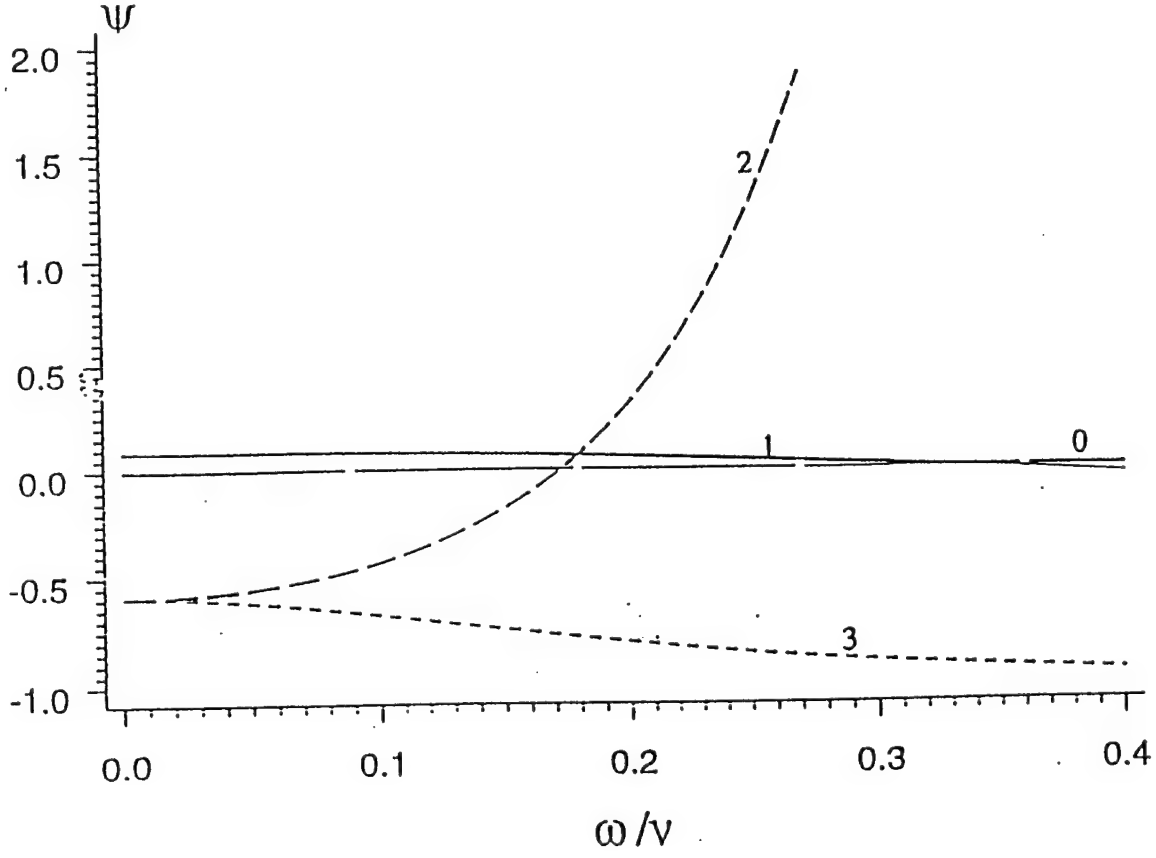
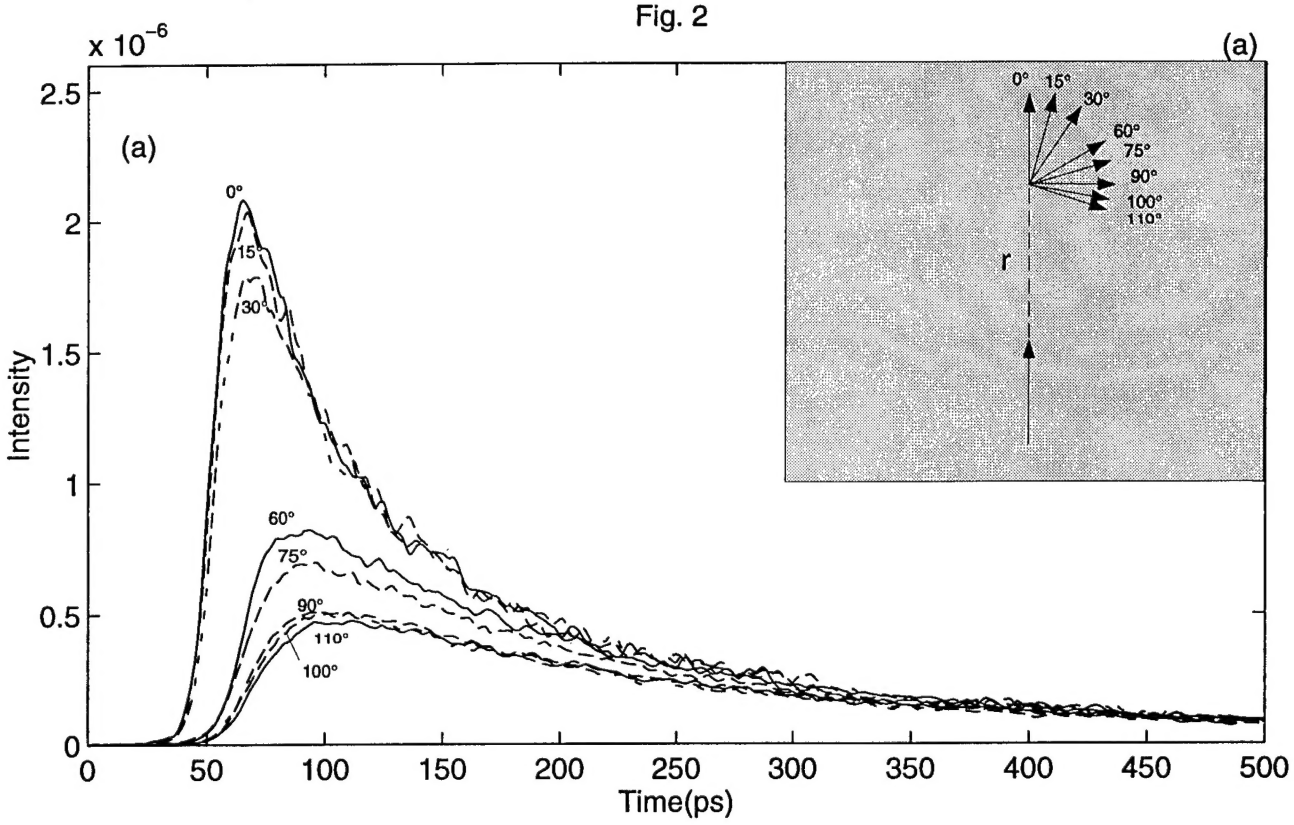


Fig. 2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Time(ps)
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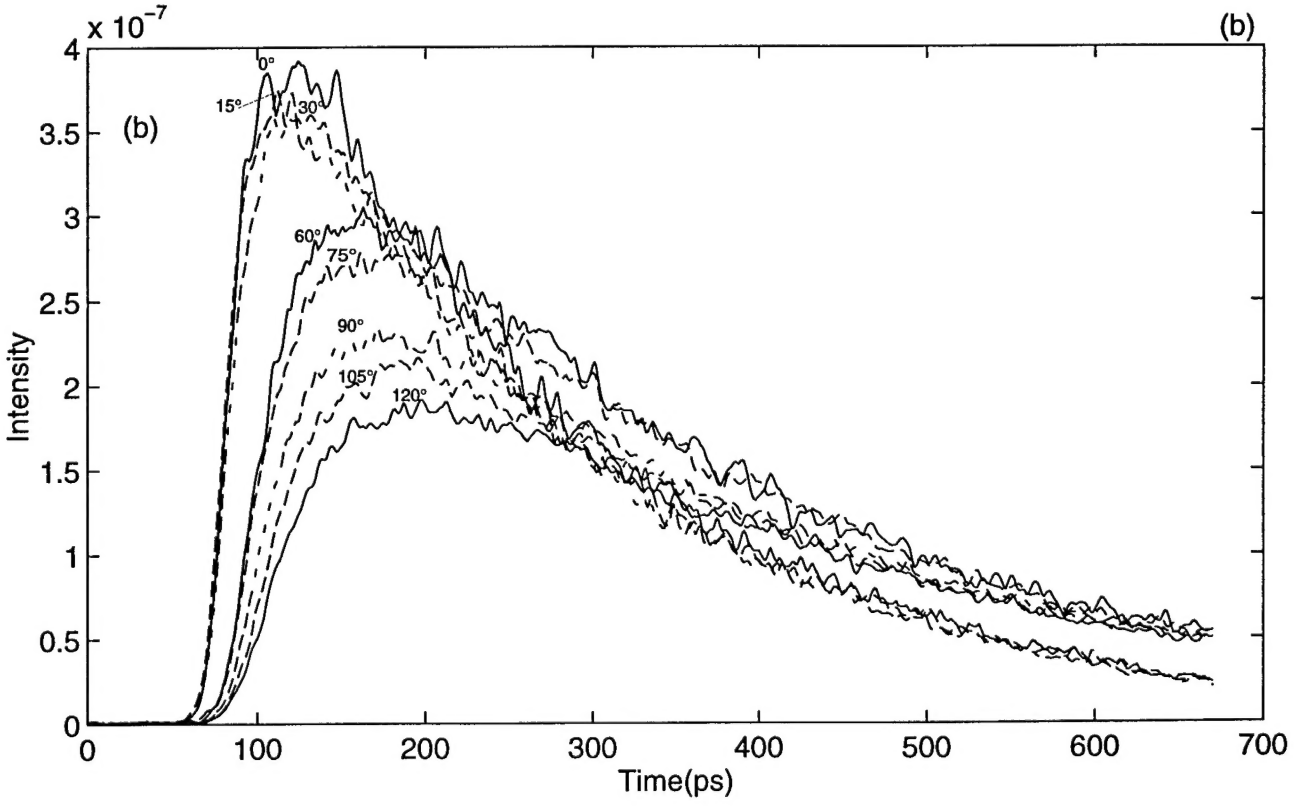
15°
30°
60°
75°
90°
110°
100°
r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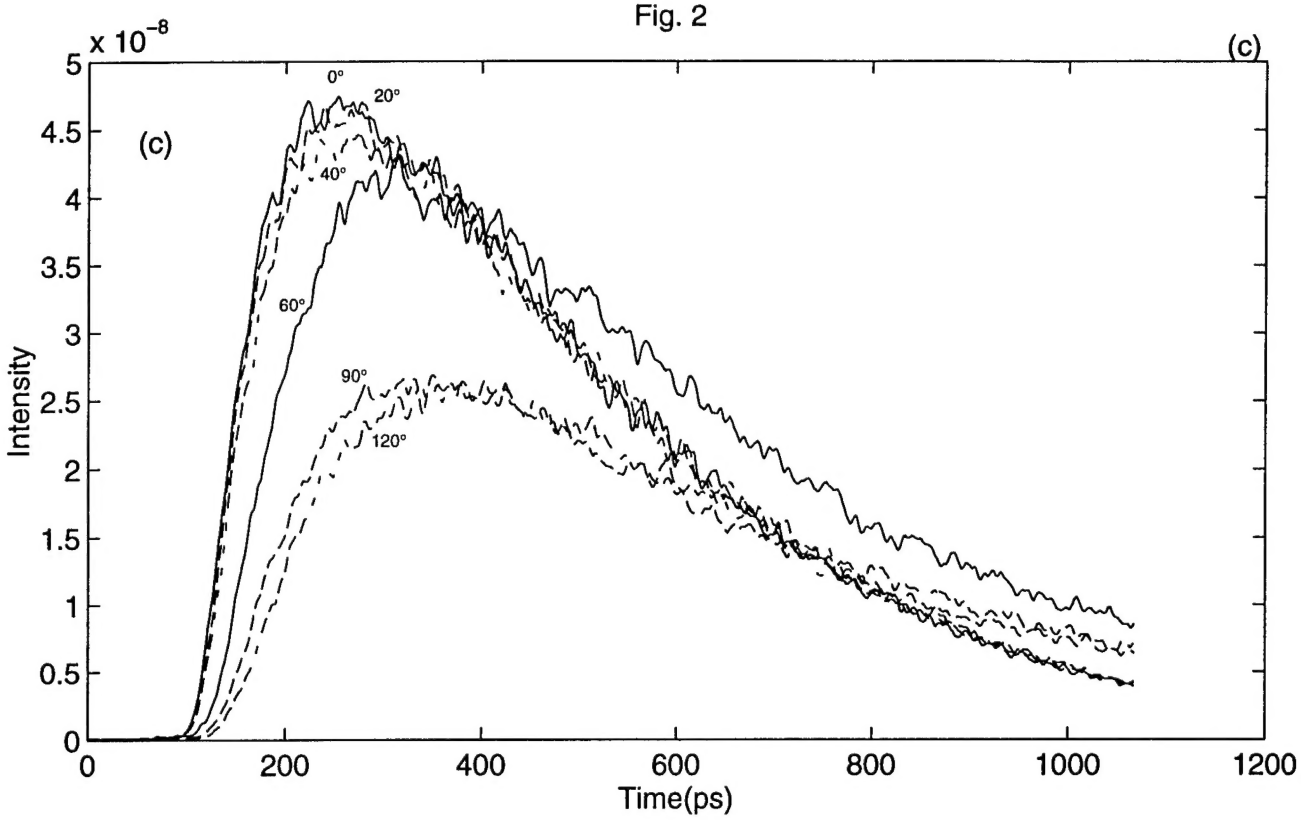
30°
60°
75°
90°
105°
120°

Fig. 2


x 10^-8
(c)
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40°
60°
90°
120°
Intensity
Time(ps)
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2.5
3
3.5
4
4.5
5
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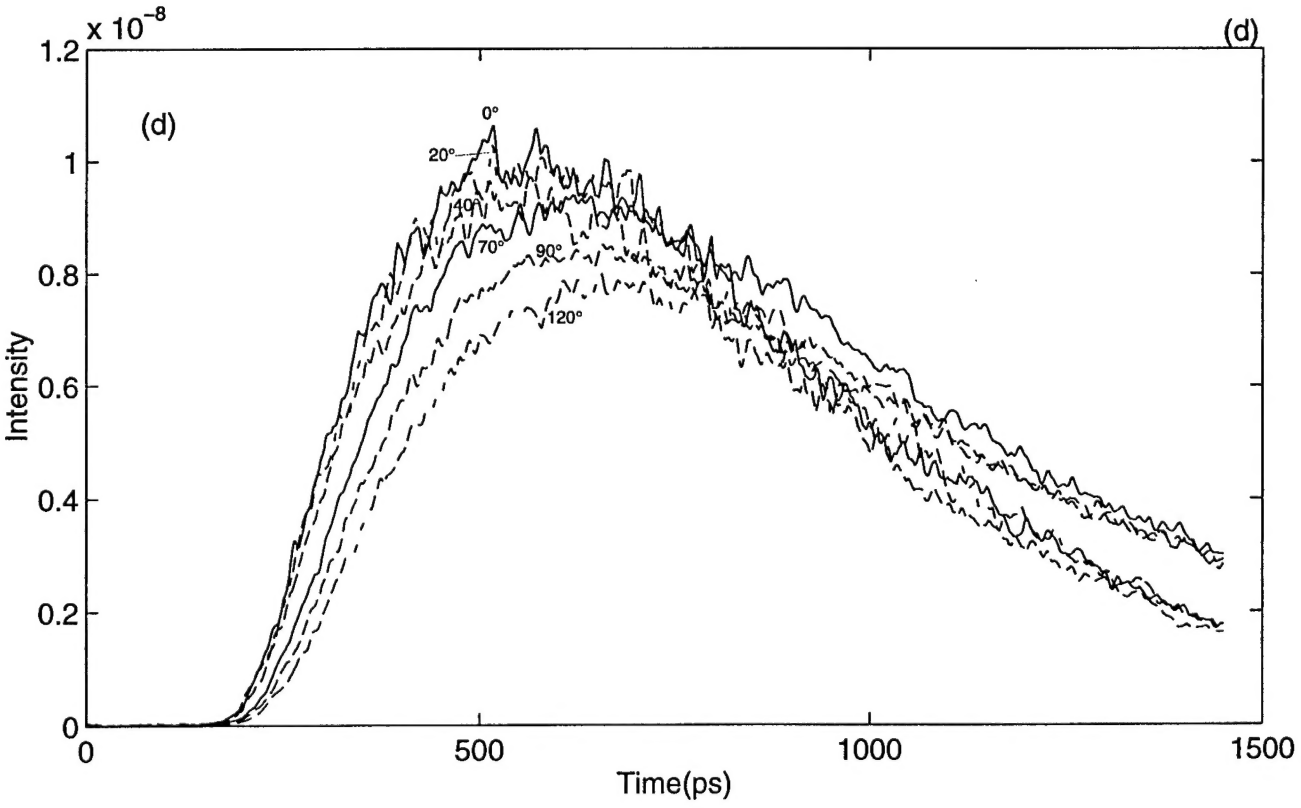
400
600
800
1000
1200


x 10^-8
(d)
0°
20°
40°
70°
90°
120°
Intensity
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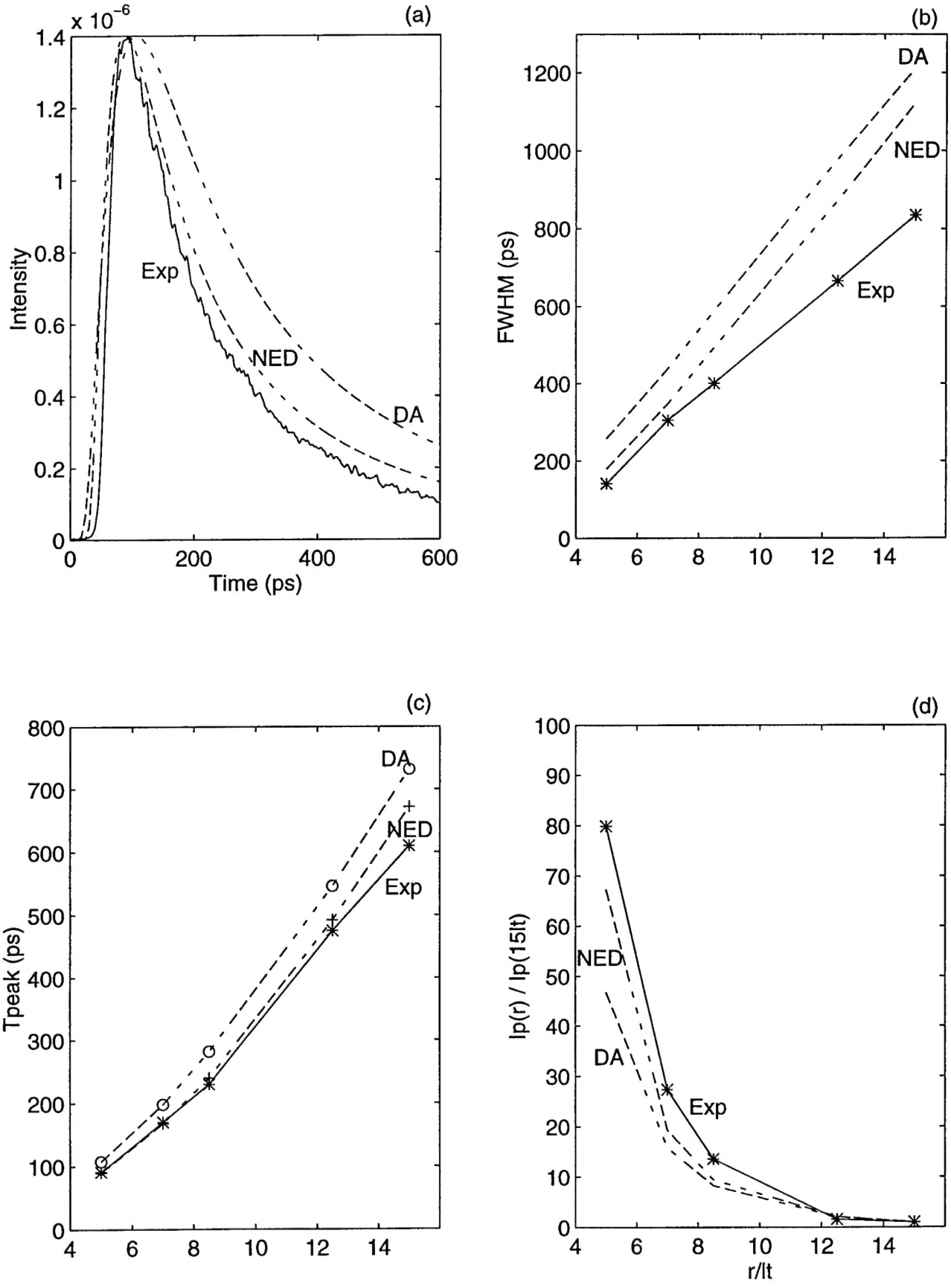
1.2
0
500
1000
1500

Fig. 3


(a)
x 10^-6
Intensity
Time (ps)
Exp
NED
DA
(b)
FWHM (ps)
DA
NED
Exp
(c)
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DA
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r/lt
NED
DA
Exp
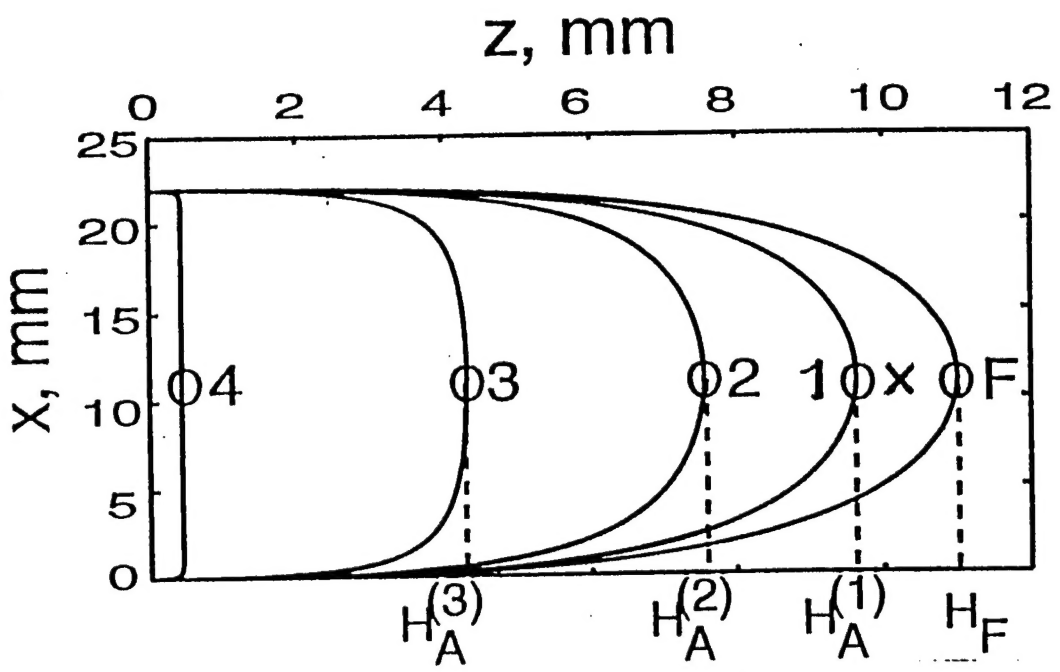
Figure 4